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Exceptional Case

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AA amyloidosis in the renal allograft: a report of two cases and review of the literature

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Abstract
AA amyloidosis is a disorder characterized by the abnormal formation, accumulation and systemic deposition of fibrillary material that frequently involves the kidney. Recurrent AA amyloidosis in the renal allograft has been documented in patients with tuberculosis, familial Mediterranean fever, ankylosing spondylitis, chronic pyelonephritis and rheumatoid arthritis. De novo AA amyloidosis is rarely described. We report two cases of AA amyloidosis in the renal allograft. Our first case is a 47-year-old male with a history of ankylosing spondylitis who developed end-stage renal disease reportedly from tubulointerstitial nephritis from non-steroidal anti-inflammatory agent use. A biopsy was never performed. One year after transplantation, AA amyloidosis was identified in the femoral head and 8 years post-transplantation, AA amyloidosis was identified in the renal allograft. He was treated with colchicine and adalimumab and has stable renal function at 1 year-follow-up. Our second case is a 57-year-old male with a long history of intravenous drug use and hepatitis C infection who developed end-stage kidney disease due to AA amyloidosis. Our second patient's course was complicated by renal adenovirus, pulmonary aspergillosis and hepatitis C with AA amyloidosis subsequently being identified in the allograft 2.5 years post-transplantation. Renal allograft function remains stable 4-years post-transplantation. These reports describe clinical and pathologic features of two cases of AA amyloidosis presenting with proteinuria and focal involvement of the renal allograft.

Keywords: AA amyloidosis; kidney transplant; post transplant

Introduction

Reactive systemic or AA amyloidosis is a disorder characterized by the abnormal formation and accumulation of extracellular fibrillary material with a resultant compromise of organ function. In the post-transplant population, a disease entity is referenced as either 'de novo' or 'recurrent' in its presentation. A de novo process refers to an entity that was not present in the patient prior to the transplant; whereas, 'recurrence' refers to a disease entity that was present before transplantation. Recurrent AA amyloid in the renal allograft has been well described [1–6]. Recurrence in the setting of chronic infection is not well documented. De novo AA amyloidosis has been rarely reported [7]. The long-term consequences of amyloid deposition on the renal allograft remain unknown. Experience reported in the literature suggests a fairly benign renal outcome in those patients with recurrent amyloid of the renal allograft. We report here two interesting cases of AA amyloidosis in the renal allograft. The first case is presented as 'potentially' de novo amyloid deposition in association with ankylosing spondylitis. Our second case reviews a case of recurrence in association with chronic infection, which has been rarely discussed.

Case reports

Case 1

Our first case is that of a 47-year-old male with a 20-year history of ankylosing spondylitis and long-standing hypertension. From his medical history, his native kidney dysfunction was attributed to tubulointerstitial nephritis from long-term use of anti-inflammatory agents. A biopsy was never performed. He received a living-related kidney transplant and was stable for ~8 years, with serum creatinines ranging from 0.9 to 1.1 mg/dL. The serum creatinine subsequently rose to levels ranging 1.7–1.9 mg/dL over a period of a few weeks prior to the biopsy. His baseline immunosuppressive medications consisted of mycophenolate mofetil 500 mg b.i.d. and tacrolimus 0.5 mg b.i.d. Physical examination findings during this time were significant for flexion deformity and decreased range of motion of the cervical spine. A kidney transplant biopsy was performed. At the time of biopsy, a chemistry panel was reported as follows: sodium 142 mmol/L, potassium 6 mmol/L, chloride 107 mmol/L, bicarbonate 27 mmol/L, blood urea nitrogen 35 mg/dL, creatinine 1.7 mg/dL, calcium 9 mg/dL and phosphorus 4.1 mg/dL. A complete blood count

was documented as follows: white blood cells 6.1 K/μL, hemoglobin 11.7 g/dL, hematocrit 37.8% and platelets 323 K/μL. Parathyroid hormone level was 94 pg/mL (Target range 35–70 pg/mL). Two months prior to the biopsy, a protein/creatinine ratio of 0.21 was noted.

Renal allograft histology. Six of 26 glomeruli (23%) exhibited amorphous eosinophilic, weakly periodic acid-Schiff-positive material around the hilum and focally in the mesangium and capillary walls (Figure 1A). Fourteen glomeruli were globally sclerosed. The material was also present in the arterioles and in several arteries, associated with extensive smooth muscle dropout and myxoid changes (Figure 1A). The arterial, arteriolar, capillary and mesangial amorphous material was Congo red positive (Figure 1B) and demonstrated apple-green birefringence under polarized light. On direct immunofluorescence, there was non-specific staining for IgG, IgA, IgM, kappa and lambda light chains. Indirect immunofluorescence staining for C4d was negative. Electron microscopy revealed fibrillar deposits in mesangial areas that were non-branching and randomly arranged, measuring up to 12 nm in thickness. Immunoperoxidase staining using a monoclonal antibody to AA amyloid (Dako, Carpinteria, CA) revealed strong reactivity in sites of amyloid deposition (Figure 1C).

Follow-up and treatment: Case 1. Following the diagnosis of AA amyloid, further tests revealed a C-reactive protein (CRP) of 14 mg/dL (ref. 0.0–0.9 mg/dL) and a rheumatoid factor of 11 units. Serologic tests for hepatitis B surface antigen and hepatitis C antibody were negative. Anti-nuclear antibody and anti-SSA/SSB titers were within normal limits.

A kidney transplant biopsy performed 1 day after renal transplantation demonstrated acute tubular necrosis without evidence of amyloidosis. However, a left hip arthroplasty performed 1 year after kidney transplantation revealed AA amyloid involving the arteries of the head of femur. The amyloid deposits were only identified on retrospective review of the tissue after identification of amyloid deposits in the allograft biopsy. The patient went on to receive colchicine and was started on adalimumab. Two months after initiation of adalimumab, the serum creatinine was 1.9 mg/dL, erythrocyte sedimentation rate (ESR) 10 mm/h and CRP <3 mg/L and the urinary protein/creatinine ratio was 0.28.

Case 2

Our second case involved a 57-year-old male with a long history of diabetes mellitus, intravenous drug use, hypertension and chronic hepatitis C infection. He received a live donor kidney transplant from his wife. End-stage kidney disease was attributed to AA amyloid. Serum creatinine values after transplantation ranged from 1.1 to 1.3 mg/dL. At 5 months, the serum creatinine rose slowly to 2.0 mg/dL. A kidney transplant biopsy demonstrated adenovirus infection with granulomatous interstitial nephritis. After treatment with cidofovir, the creatinine stabilized to ~1.3–1.5 mg/dL. Three years later, pulmonary aspergillosis was identified and treated with itraconazole. A thoracotomy and resection of the left apical pulmonary lesion were also performed. Evidence of mycobacterial infection was absent during this time. The serum creatinine remained stable at 1.3–1.5 mg/dL. Two years later, a hepatitis C viral load was documented at 51 628 IU/mL and the serum creatinine was elevated at 2.5 mg/dL. Urinalysis revealed 4+ proteinuria. A second kidney transplant biopsy was performed. No CRP or ESR assays were obtained during this time.

Renal allograft histology. Two of 19 glomeruli (10.5%) had segmental eosinophilic weakly periodic acid-Schiff positive matrix accumulation within the glomerular tufts around the hila. Four glomeruli were globally sclerosed. Atrophic tubules with marked thickening of the basement membranes were seen. Arteries and arterioles had extensive smooth muscle dropout and myxoid degeneration mimicking calcineurin inhibitor toxicity (Figure 1D). A Congo red stain for amyloidosis revealed focal and segmental positivity in glomeruli, in the interstitium around the tubules and staining of the walls of the arteries and arterioles (Figure 1E). Immunohistochemical staining (as above) verified the diagnosis of AA amyloidosis (Figure 1F).

Follow-up and treatment: Case 2. The patient's development of numerous infections post-transplant was thought to contribute to the eventual formation of amyloid. Hepatitis C appeared to be the only clinically significant ongoing chronic infection throughout the post-transplant course. Treatment of hepatitis C could not be actively addressed given the potential for induction of rejection by interferon. After the biopsy, the creatinine hovered around 1.4–1.7 mg/dL with a protein/creatinine ratio of 0.2. A prerenal state with blood pressures below his normal was possibly the cause of the documented creatinine of 2.5 mg/dL. A repeat hepatitis polymerase chain reaction a few months later revealed Hepatitis C RNA of 42 374 IU/mL.

Discussion

AA amyloidosis is a disorder characterized by the abnormal formation, accumulation and systemic deposition of fibrillary material that frequently involves the kidney. The amyloidogenic precursor protein, serum amyloid A (SAA), is synthesized by the liver in response to proinflammatory cytokines and is then transported in the plasma as a component of high-density lipoprotein. Only those inflammatory conditions with a clinically significant 'sustained' acute-phase reactant response are subject to the formation of amyloid. It is proposed that the mechanism of formation follows a series of steps [8], with the process beginning with the abnormal folding of SAA protein (an acute phase reactant) [8]. An amino acid mutation, an environmental factor, a proteolytic cleavage event or certain pathogenic intrinsic properties in the presence of high concentrations of SAA are then thought to contribute to the abnormal process of folding [8]. SAA is then internalized by macrophages with subsequent C-terminal cleavage of SAA to AA and intracellular initiation of fibril formation [8]. It is the final interaction of SAA/AA fibrils with glycosaminoglycans and other moieties, including serum amyloid P component (SAP) that seems to be crucial, with glycosaminoglycans and SAP component being proposed key players in the formation, deposition and stabilization of amyloid [8]. As a final step, fibrils are deposited in the extracellular space [8].

Target AA amyloid treatment strategies have been aimed at the underlying disease. More recent studies have focused on the substance of amyloid itself. In a case report by Escalante [9], colchicine was evaluated, with the proposed mechanism of action being inhibition of the production of SAA protein [9]. Tumor necrosis factor alpha antagonists

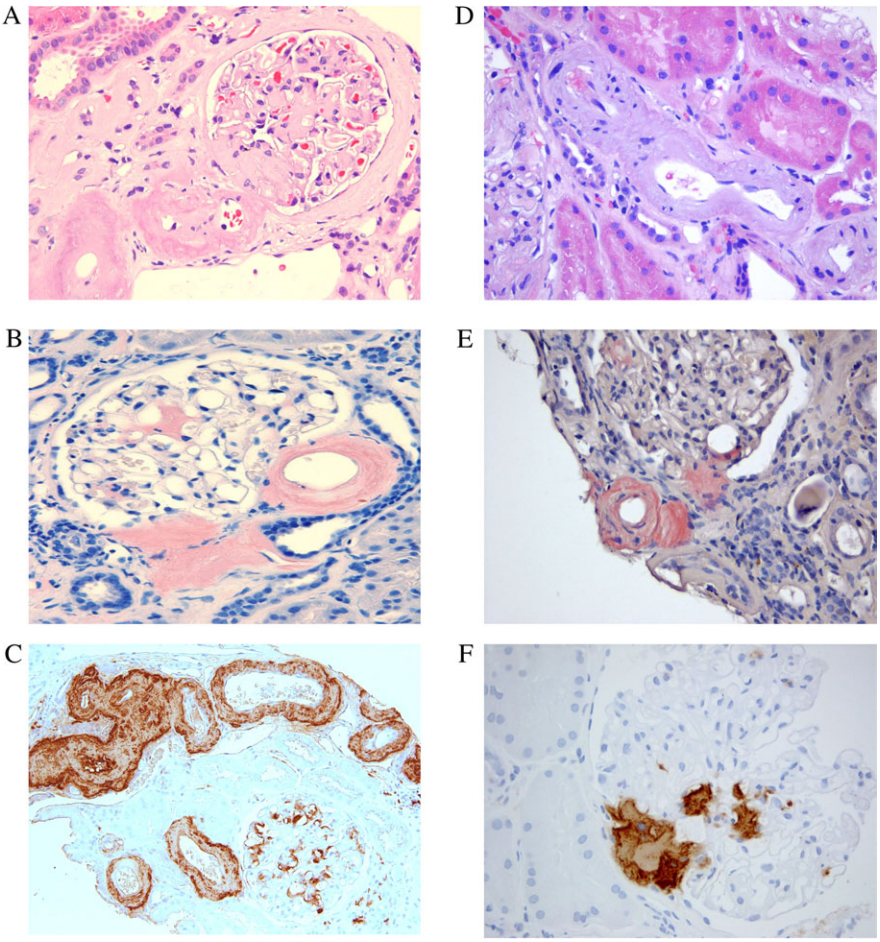

Fig. 1. (**A**) Acellular eosinophilic material in the mesangium, hilus, arterioles and in the interstitium. (**B**) Hilar and mesangial Congo red positivity. (**C**) Immunohistochemistry for AA amyloid protein reveals deposits in the mesangium, hilus and in arterial walls. (**D**) Arterial smooth muscle dropout with myxoid change. (**E**) Congo red-positive deposits in the mesangium, hilus and arteriole. (**F**) Hilar and mesangial staining for AA amyloidosis by immunohistochemistry.

have also been considered for potential treatment of AA amyloid [10], with the mechanism of action here being much more complex. More recently, eprodisate and even lovastatin have been proposed as potential treatment strategies [11, 12].

The recurrence of AA amyloidosis in the renal allograft is well documented [1–5] with one of the earliest cases being seen in 1977 in a patient with familial Mediterranean fever [4]. Recurrence has also been seen in patients with tuberculosis, ankylosing spondylitis and rheumatoid arthritis [1–3, 5]. Recurrence of amyloidosis secondary to chronic infections is rarely documented and only reported in the setting of tuberculosis and chronic urinary tract infections (UTIs) [1, 15]. In all cases, there was continued evidence of an inflammatory condition after transplantation (either in the form of their continued clinically active primary disease or development of clinically significant infections post-transplant). Although amyloid deposition was present (in some cases involving more than just the renal allograft), renal function was preserved in all with minimal to no proteinuria noted. It also appeared that in most cases, the structures most affected by allograft amyloid deposition were the blood vessels. Interestingly, all patients were only maintained on azathioprine and prednisone.

De novo documentation of AA amyloid in the transplanted kidney has rarely been seen [7]. Its only documentation has been in that of a patient with end-stage kidney disease secondary to Autosomal Dominant Polycystic Kidney Disease. Though amyloid deposition was eventually found in this patient, it was seen almost 16 years post-transplant! An allograft biopsy demonstrated AA amyloid deposition of 'all compartments' of the renal allograft. No conclusions can be drawn from what little is known.

Conclusion

Recurrent or de novo amyloidosis in the transplanted kidney has not been well documented and is not entirely understood. The current cases are consistent with potentially de novo presentation of AA amyloid in the renal allograft in ankylosing spondylitis and also introduce the potential association of recurrence in the setting of chronic infections other than that of tuberculosis and chronic UTIs. Recurrence of amyloid is not necessarily detrimental to the renal allograft. The major compartment affected in recurrence primarily appears to be the renal blood vessels with sparing of other structures in most cases. In the few cases of de novo presentation, the renal structures involved were not limited to the blood vessels. In both cases, the creatinine was found to be elevated but only after several years post-transplant, and there was proteinuria (mild in one and severe in one) and focal involvement of the glomeruli (10.5 and 23%)

and blood vessels. Each has stable allograft function on follow-up.

Conflict of interest statement. None declared.

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